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URGENT MATTERS CONCERNING THE IMPLEMENTATION OF INTERNATIONAL DRUG CONTROL TREATIES

Note by the Secretary-General

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I. CONSIDERATION OF NOTIFICATIONS RECOMMENDING SCHEDULING UNDER THE SINGLE CONVENTION ON NARCOTIC DRUGS, 1961, AS AMENDED BY THE 1972 PROTOCOL AMENDING THE SINGLE CONVENTION ON NARCOTIC DRUGS, 1961

Alpha-methylthiofentanyl, para-fluorofentanyl, beta-hydroxyfentanyl, beta-hydroxy-3-methylfentanyl, thiofentanyl and 3-methylthiofentanyl

1. Pursuant to article 3, paragraphs 3(iii) and 5, of the Single Convention on Narcotic Drugs, 1961, as amended by the 1972 Protocol to that Convention, 1/ the Director-General of the World Health Organization notified the Secretary-General by notes dated 3 June 1989 that WHO was of the opinion that the six substances alpha-methylthiofentanyl (N-[1-[1-methyl-2-(2-thienyl) ethyl]-4-piperidyl]propionanilide), para-fluorofentanyl (4'-fluoro-N-(1-phenethyl-4-piperidyl)propionanilide), beta-hydroxyfentanyl (N-[1-(beta-hydroxyphenethyl)-4-piperidyl]propionanilide), beta-hydroxy-3-methylfentanyl (N-[1-(beta-hydroxyphenethyl)-3-methyl-4-piperidyl]propionanilide), thiofentanyl (N-[1-[2-(2-thienyl)ethyl]-4-piperidyl]propionanilide) and 3-methylthiofentanyl (N-[3-methyl-1-[2-(2-thienyl)ethyl]-4-piperidyl]propionanilide) should be included in Schedules I and IV of that Convention. These six substances, so-called "designer drugs", are analogues of fentanyl, a substance already under international control in Schedule I of the Convention. The text of those notifications, as well as the substantiating evidence in support of the recommendations contained in the twenty-sixth report of the WHO Expert Committee on Drug Dependence, are reproduced in annex I to the present document. In accordance with the provisions of article 3, paragraph 2, of the Single Convention, the Secretary-General transmitted to all Governments, by a note dated 22 August 1989, the text of the six notifications. In response to that note, as of 24 November 1989, three Governments (Australia, Ecuador and Turkey) expressed agreeement with the inclusion of the six substances in Schedules I and IV.

2. The six notifications by the Director-General of WHO are now before the Commission for consideration, in accordance with the provisions of article 3, paragraphs 3(iii) and 5, of the Single Convention.

Article 3, paragraph 3(iii), reads as follows:

> "If the World Health Organizations finds that the substance is liable to similar abuse and productive of similar ill effects as the drugs in Schedule I or Schedule II or is convertible into a drug, it shall communicate that finding to the Commission which may, in accordance with the recommendation of the World Health Organization, decide that the substance shall be added to Schedule I or Schedule II."

Article 3, paragraph 5, reads as follows:

> "If the World Health Organization finds that a drug in Schedule I is particularly liable to abuse and to produce ill effects (paragraph 3) and that such liability is not offset by substantial therapeutic advantages not possessed by substances other than drugs in Schedule IV, the Commission may, in accordance with the recommendation of the World Health Organization, place that drug in Schedule IV."

3. At this stage, the Commission should therefore decide whether or not it wishes to include alpha-methylthiofentanyl, para-fluorofentanyl, beta-hydroxyfentanyl, beta-hydroxy-3-methylfentanyl, thiofentanyl and 3-methylthiofentanyl in Schedules I and IV of the Single Convention on Narcotic Drugs, 1961, as amended by the 1972 Protocol to that Convention, or, if not, what other action, if any, is required.

II. CONSIDERATION OF NOTIFICATIONS RECOMMENDING SCHEDULING OR RESCHEDULING UNDER THE CONVENTION ON PSYCHOTROPIC SUBSTANCES, 1971

Delta-9-tetrahydrocannabinol

4. Pursuant to article 2, paragraph 1, of the Convention on Psychotropic Substances 1971, 2/ the Government of the United States of America sent a notification to the Secretary-General informing him that, in its opinion, delta-9-tetrahydrocannabinol (delta-9-THC), which is at present listed in Schedule I of the Convention, should be transferred from that Schedule to Schedule II. The notification by the Government of the United States of America was transmitted to all Governments under cover of a note from the Secretary-General dated 28 January 1988.

5. The text of the notification and the relevant information submitted in support of that notification are reproduced in annex II. The Secretary-General also transmitted a copy of the notification to WHO, in accordance with the provisions of article 2, paragraph 2, of the Convention. In order to assist WHO in the examination of this proposal, Governments were requested to submit data on delta-9-THC to the Secretary-General for consideration by the WHO Expert Committee on Drug Dependence at its 26th meeting.

6. In accordance with the provisions of article 2, paragraph 4, of the Convention, the Director-General of WHO notified the Secretary-General by a note dated 3 June 1989 that WHO had reviewed information pertaining to dronabinol (INN), defined as (6aR,10aR)-6a,7,8,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]-pyran-1-ol or (-)-trans-delta-9-tetrahydrocannabinol, which is currently in Schedule I of that Convention and is listed as one of the stereochemical variants of delta-9-tetrahydrocannabinol, and recommended that it should be transferred from Schedule I to Schedule II of the Convention. The text of the notification, and of the substantiating evidence produced in support of the recommendation of the Expert Committee are reproduced in annex III.

7. Following receipt of that notification, the Secretary-General sent to all Governments a note dated 21 August 1989. In that note the Secretary-General invited Governments to indicate any economic, social, legal, administrative or other factors that they might consider relevant to the question of the possible rescheduling of dronabinol. In response to that note, eight replies (from Australia, Ecuador, Finland, German Democratic Republic, Morocco, Spain, Thailand and Turkey) had been received by 24 November 1989. Of these, five (Australia, Finland, Morocco, Thailand and Turkey) expressed agreement with, or had no objection to, the WHO proposal. Two (Ecuador and Spain) indicated that some administrative problems might arise if the substance were to be transferred from Schedule I to Schedule II, but they did not express any objection to the proposal. One Government (German Democratic Republic) was of the opinion that the substance should not be transferred to Schedule II because of health and social problems arising from the abuse of cannabis and

THC. The data collected by the Secretary-General in response to his previous note, of 28 January 1988, is summarized in paragraphs 8-11 below.

8. As of 1 August 1988, replies had been received by the Division of Narcotic Drugs from 39 countries and one territory, as follows: Argentina, Australia, Austria, Bahrain, Belgium, Botswana, Burma, Canada, Costa Rica, Cuba, Dominican Republic, Finland, France, German Democratic Republic, Guatemala, Hungary, Iraq, Japan, Jordan, Kenya, Luxembourg, Malaysia, Mexico, Mozambique, the Netherlands, Netherlands Antilles, Qatar, Republic of Korea, Romania, Rwanda, Singapore, South Africa, Spain, Switzerland, Thailand, Turkey, United Kingdom of Great Britain and Northern Ireland, United States of America, Vanuatu and Zimbabwe.

9. Delta-9-tetrahydrocannabinol was reported as available in Bahrain (but not widely used in clinical practice), in the Netherlands and the United Kingdom (for scientific research only) and in the United States (in preparation form, on prescription). Burma, Romania, Rwanda, Switzerland and Turkey were in agreement with the proposal to transfer the substance from Schedule I to Schedule II. Bahrain was of the opinion that the substance should remain in Schedule I. The Dominican Republic and Iraq acknowledged receipt of the Secretary-General's note without further comments.

10. No Government reported public health or social problems arising from abuse of the substance. Belgium reported that it was very difficult to say whether there was any abuse of the substance on its own, because it was the principal psycho-active component of cannabis that was widely abused. Costa Rica reported that abuse of the substance occurred only as a main component of cannabis. The German Democratic Republic reported that the substance was under national control and, because of its high potential for abuse, should remain in Schedule I. The United States reported one mention in the Drug Abuse Warning Network* system associated with the commercially available delta-9-THC product between 1984 and 1988.

11. The United Kingdom reported one attempt to synthesize delta-9-THC (using citral and olivetol) in 1987. The United States reported that no seizure data were available on the approved delta-9-THC product. The United Kingdom also reported one case involving illicit purchase of 20.5 mg dosage units of the preparation containing the substance, in the System to Retrieve Information from Drug Evidence (STRIDE)** for the period from 1 January 1986 to 31 March 1988. In addition, six reports of theft involving 228 dosage units (1,202 g) of the preparation containing the substance were received by the Drug Enforcement Administration (DEA) in 1987. The loss of 1.04 g of delta-9-THC from a research laboratory was also reported to DEA in 1987. No Government reported any seizures of the substance in a pure form.

12. The question of the possible transfer of dronabinol from Schedule I to Schedule II of the 1971 Convention is now before the Commission, pursuant to article 2, paragraph 6, of the Convention, which reads as follows:

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*Indicates emergency room members in relation to selected substances.

**STRIDE was devised to provide data for drug intelligence, early warning, drug control, planning and management. The system has been used to detect the appearance of new drugs of abuse, to collect data to determine the extent of abuse, to detect unusual occurrences and to report other matters of drug intelligence.

"If a notification under paragraph 1 relates to a substance already listed in one of the Schedules, the World Health Organization shall communicate to the Commission its new findings, any new assessment of the substance it may make in accordance with paragraph 4 and any new recommendations on control measures it may find appropriate in the light of that assessment. The Commission, taking into account the communication from the World Health Organization as under paragraph 5 and bearing in mind the factors referred to in that paragraph, may decide to transfer the substance from one Schedule to another or to delete it from the Schedules."

At this stage, the Commission should therefore decide whether or not it wishes to transfer dronabinol from Schedule I to Schedule II of the 1971 Convention, or, if not, what other action, if any, is required.

N-hydroxy MDA, N-ethyl MDA, 4-methylaminorex and midazolam

13. Pursuant to article 2, paragraphs 1 and 4, of the Convention on Psychotropic Substances, 1971, 2/ the Director-General of WHO notified the Secretary-General, by notes dated 3 June 1989, that WHO was of the opinion that midazolam (8-chloro-6-(o-fluorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepine) should be included in Schedule IV of that Convention and that the three substances N-hydroxy MDA ((±)-N-[alpha-methyl-3,4-(methylenedioxy)phenethyl]hydroxylamine), N-ethyl MDA ((±)-N-ethyl-alpha-methyl-3,4-(methylenedioxy)phenethylamine) and 4-methylaminorex ((±)-cis-2-amino-4-methyl-5-phenyl-2-oxazoline) should be included in Schedule I of the Convention. In accordance with the provisions of article 2, paragraph 2, of the Convention, the Secretary-General transmitted to all Governments, by a note dated 18 August 1989, the text of the four notifications, which is reproduced in annex IV, together with substantiating evidence submitted in support of the recommendation contained in the twenty-sixth report of the Expert Committee on Drug Dependence. In his note, the Secretary-General invited Governments to indicate any economic, social, legal, administrative or other factors Governments might consider relevant to the question of the possible scheduling of those substances.

14. In response to that note, as of 24 November 1989, 11 Governments (Australia, Chile, Ecuador, Finland, German Democratic Republic, India, Morocco, Papua New Guinea, Spain, Thailand and Turkey) expressed agreement with, or had no objection to, the WHO proposal. Two (Chile and Ecuador) reported that midazolam was available in preparation form in their countries. One (Finland) reported two cases of death in 1986 and four in 1987 related to the use of midazolam. Some abuse of midazolam was reported by one Government (Thailand).

15. The notifications by the Director-General of WHO are now before the Commission for consideration in accordance with the provisions of article 2, paragraph 5, of the Convention on Psychotropic Substances. 2/ That paragraph reads:

"The Commission, taking into account the communication from the World Health Organization, whose assessments shall be determinative as to medical and scientific matters, and bearing in mind the economic, social, legal, administrative and other factors it may consider relevant, may add the substance to Schedule I, II, III or IV. The Commission may seek further information from the World Health Organization or from other appropriate sources."

At this stage, the Commission should therefore decide whether or not it wishes to include midazolam in Schedule IV of the 1971 Convention and N-hydroxy MDA, N-ethyl MDA and 4-methylaminorex in Schedule I of that Convention, following the recommendation of WHO, or, if not, what other action, if any, is required.

Notes

1/ See United Nations publication, Sales No. E.77.XI.3.

2/ See United Nations publication, Sales No. E.78.XI.3 and amendment.

Annex I

NOTIFICATIONS FROM THE DIRECTOR-GENERAL OF THE WORLD HEALTH ORGANIZATION CONCERNING ALPHA-METHYLTHIOFENTANYL, PARA-FLUOROFENTANYL, BETA-HYDROXYFENTANYL, BETA-HYDROXY-3-METHYLFENTANYL, THIOFENTANYL AND 3-METHYLTHIOFENTANYL

Alpha-methylthiofentanyl

The Director-General of the World Health Organization presents his compliments to the Secretary-General of the United Nations, and with reference to the Twenty-sixth Report of the WHO Expert Committee on Drug Dependence, has the honour to inform him that the World Health Organization, in conformity with article 3, paragraphs 3(iii) and 5, of the Single Convention on Narcotic Drugs, 1961 and of that Convention as amended by the 1972 Protocol, has found that N-[1-[1-methyl-2-(2-thienyl)ethyl]-4-piperidyl]propionanilide, which is also known as alpha-methylthiofentanyl, is liable to similar abuse and productive of similar ill-effects as the drugs in Schedule I of these Conventions. Alpha-methylthiofentanyl has no known therapeutic use. It is thus recommended that alpha-methylthiofentanyl be added to Schedules I and IV of those Conventions.

Para-fluorofentanyl

The Director-General of the World Health Organization presents his compliments to the Secretary-General of the United Nations, and with reference to the Twenty-sixth Report of the WHO Expert Committee on Drug Dependence, has the honour to inform him that the World Health Organization, in conformity with article 3, paragraphs 3(iii) and 5, of the Single Convention on Narcotic Drugs, 1961 and of that Convention as amended by the 1972 Protocol, has found that 4'-fluoro-N-(1-phenethyl-4-piperidyl)propionanilide, which is also known as para-fluorofentanyl, is liable to similar abuse and productive of similar ill effects as the drugs in Schedule I of these Conventions. Para-fluorofentanyl has no known therapeutic use. It is thus recommended that para-fluorofentanyl be added to Schedules I and IV of those Conventions.

Beta-hydroxyfentanyl

The Director-General of the World Health Organization presents his compliments to the Secretary-General of the United Nations, and with reference to the Twenty-sixth Report of the WHO Expert Committee on Drug Dependence, has the honour to inform him that the World Health Organization, in conformity with article 3, paragraphs 3(iii) and 5, of the Single Convention on Narcotic Drugs, 1961 and of that Convention as amended by the 1972 Protocol, has found that N-[1-(beta-hydroxyphenethyl)-4-piperidyl]propionanilide, which is also known as beta-hydroxyfentanyl, is liable to similar abuse and productive of similar ill effects as the drugs in Schedule I of these Conventions. Beta-hydroxyfentanyl has no known therapeutic use. It is thus recommended that beta-hydroxyfentanyl be added to Schedules I and IV of those Conventions.

Beta-hydroxy-3-methylfentanyl

The Director-General of the World Health Organization presents his compliments to the Secretary-General of the United Nations, and with reference to the Twenty-sixth Report of the WHO Expert Committee on Drug Dependence, has the honour to inform him that the World Health Organization, in conformity with article 3, paragraphs 3(iii) and 5, of the Single Convention on Narcotic Drugs, 1961 and of that Convention as amended by the 1972 Protocol, has found

that N-[1-(beta-hydroxyphenethyl)-3-methyl-4-piperidyl]propionanilide, which is also known as beta-hydroxy-3-methylfentanyl, is liable to similar abuse and productive of similar ill effects as the drugs in Schedule I of these Conventions. Beta-hydroxy-3-methylfentanyl has no known therapeutic use. It is thus recommended that beta-hydroxy-3-methylfentanyl be added to Schedules I and IV of those Conventions.

Thiofentanyl

The Director-General of the World Health Organization presents his compliments to the Secretary-General of the United Nations, and with reference to the Twenty-sixth Report of the WHO Expert Committee on Drug Dependence, has the honour to inform him that the World Health Organization, in conformity with article 3, paragraphs 3(iii) and 5, of the Single Convention on Narcotic Drugs, 1961 and of that Convention as amended by the 1972 Protocol, has found that N-[1-[2-(2-thienyl)ethyl]-4-piperidyl]propionanilide, which is also known as thiofentanyl, is liable to similar abuse and productive of similar ill effects as the drugs in Schedule I of these Conventions. Thiofentanyl has no known therapeutic use. It is thus recommended that thiofentanyl be added to Schedules I and IV of those Conventions.

3-Methylthiofentanyl

The Director-General of the World Health Organization presents his compliments to the Secretary-General of the United Nations, and with reference to the Twenty-sixth Report of the WHO Expert Committee on Drug Dependence, has the honour to inform him that the World Health Organization, in conformity with article 3, paragraphs 3(iii) and 5, of the Single Convention on Narcotic Drugs, 1961 and of that Convention as amended by the 1972 Protocol, has found that N-[3-methyl-1-[2-(2-thienyl)ethyl]-4-piperidyl]propionanilide, which is also known as 3-methylthiofentanyl, is liable to similar abuse and productive of similar ill effects as the drugs in Schedule I of these Conventions. 3-Methylthiofentanyl has no known therapeutic use. It is thus recommended that 3-Methylthiofentanyl be added to Schedules I and IV of those Conventions.

Summary of the recommendations arising out of the twenty-sixth Expert Committee on Drug Dependence

The twenty-sixth Expert Committee on Drug Dependence met at headquarters between 17 and 22 April 1989. Since the report of this meeting will be published in due course in the Technical Report Series, this paper gives details of the recommendations made to the Director-General of WHO.

[.....]

Controlled substances analogues (designer drugs)

Fentanyl analogues

It should be noted that the compounds described in this section have a close chemical similarity to substances already controlled in Schedules I and IV of the Single Convention on Narcotic Drugs, 1961 as amended by the 1972 Protocol. These "designer drugs" represent a potentially serious international public health problem because of their relative ease of synthesis and, in some cases, their extreme potency, which makes them effective in very small amounts.

Alpha-methylthiofentanyl

Substance identification

Alpha-methylthiofentanyl (CAS 103963-66-2), chemically N-[1-[1-methyl-2-(2-thienyl)ethyl]-4-piperidyl]propionanilide, is also known as NIH 10538 and MCV 4583. There is one chiral carbon atom in the molecule, so that two stereoisomers and one racemate are possible.

Similarity to already known substances and effects on the central nervous system

Alpha-methylthiofentanyl has been classified pharmacologically as a relatively selective mu-type opioid receptor agonist with a profile similar to that of fentanyl. Its analgesic potency in rodents is at least the same as that of fentanyl and 450 to 600 times that of morphine. Its analgesic effect has a rapid onset but longer duration than fentanyl.

Dependence potential

Alpha-methylthiofentanyl substitutes completely for morphine in morphine-dependent withdrawn monkeys. The substance is about 100 times more potent than morphine in this regard. No human studies are available concerning the dependence potential of alpha-methylthiofentanyl.

Actual abuse and/or abuse liability (likelihood of abuse)

Alpha-methylthiofentanyl is one of the fentanyl analogues which have appeared in the illicit drug traffic since late 1979. Alpha-methylthiofentanyl has been identified by a Drug Enforcement Administration (USA) laboratory in drug seizures and clandestine production has been demonstrated.

Therapeutic usefulness

At present alpha-methylthiofentanyl has no known therapeutic usefulness.

Recommendation

The Committee found that there was sufficient evidence to indicate that alpha-methylthiofentanyl is liable to similar abuse as, and produces ill-effects similar to those seen with, drugs in Schedule I of the Single Convention on Narcotic Drugs, 1961 and that Convention as amended by the 1972 Protocol. The Committee rated the abuse liability of the substance as high. The degree of seriousness of the public health and social problems associated with the substance was found to be high and there is no known therapeutic usefulness. Therefore, the Committee recommended that alpha-methylthiofentanyl be controlled in Schedules I and IV of the Single Convention on Narcotic Drugs, 1961 and that Convention as amended by the 1972 Protocol.

Para-fluorofentanyl

Substance identification

Para-fluorofentanyl (CAS 90736-23-5), chemically 4'-fluoro-N-(1-phenethyl-4-piperidyl)propionanilide, is also known as NIH 10022, NIH 10491 and MCV 4323. No stereoisomers are possible.

Similarity to already known substances and effects on the central nervous system

Para-fluorofentanyl has been classified pharmacologically as a relatively selective mu-type opioid receptor agonist with a profile similar to that of fentanyl. Its analgesic potency in rodents is estimated to be 100 times that of morphine.

Dependence potential

Para-fluorofentanyl substitutes completely for morphine in morphine-dependent withdrawn monkeys. The substance is about 50-75 times more potent than morphine in this regard. No human studies are available concerning the dependence potential of para-fluorofentanyl.

Actual abuse and/or abuse liability (likelihood of abuse)

Para-fluorofentanyl is one of the fentanyl analogues which have appeared in the illicit drug traffic since late 1979. Para-fluorofentanyl has been identified by a Drug Enforcement Administration (USA) laboratory in drug seizures and clandestine production has been demonstrated.

Therapeutic usefulness

At present, para-fluorofentanyl has no known therapeutic usefulness.

Recommendation

The Committee found that there was sufficient evidence to indicate that para-fluorofentanyl is liable to similar abuse as, and produces ill-effects similar to those seen with, drugs in Schedule I of the Single Convention on Narcotic Drugs, 1961 and that Convention as amended by the 1972 Protocol. The Committee rated the abuse liability of the substance as high. The degree of seriousness of the public health and social problems associated with the substances was found to be high and there is no known therapeutic usefulness. Therefore, the Committee recommended that para-fluorofentanyl be controlled in

Schedules I and IV of the Single Convention on Narcotic Drugs, 1961 and that Convention as amended by the 1972 Protocol.

Beta-hydroxyfentanyl

Substance identification

Beta-hydroxyfentanyl (CAS 78995-10-5), chemically N-[1-(beta-hydroxyphenethyl)-4-piperidyl]propionanilide, is also known as NIH 10506 and MCV 4568. There is one chiral carbon atom in the molecule, so that two stereoisomers and one racemate are possible.

Similarity to already known substances and effects on the central nervous system

Beta-hydroxyfentanyl has been classified pharmacologically as a relatively selective mu-type opioid receptor agonist with a profile similar to that of fentanyl. Its analgesic potency in rodents is estimated to be about 50 times that of morphine. In the rhesus monkey, beta-hydroxyfentanyl acts promptly and its duration of action (120-150 minutes) is shorter than that of morphine.

Dependence potential

Beta-hydroxyfentanyl substitutes completely for morphine in morphine-dependent withdrawn monkeys. The substance is 50 times more potent than morphine in this regard. No human studies are available concerning the dependence potential of beta-hydroxyfentanyl.

Actual abuse and/or abuse liability (likelihood of abuse)

Beta-hydroxyfentanyl is one of the fentanyl analogues which have appeared in the illicit drug traffic since late 1979. Beta-hydroxyfentanyl has been identified by a Drug Enforcement Administration (USA) laboratory in drug seizures and clandestine production has been demonstrated.

Therapeutic usefulness

At present, beta-hydroxyfentanyl has no known therapeutic usefulness.

Recommendation

The Committee found that there was sufficient evidence to indicate that beta-hydroxyfentanyl is liable to similar abuse as, and produces ill-effects similar to those seen with, drugs in Schedule I of the Single Convention on Narcotic Drugs, 1961 and that Convention as amended by the 1972 Protocol. The Committee rated the abuse liability of the substance as high. The degree of seriousness of the public health and social problems associated with the substances was found to be high and there is no known therapeutic usefulness. Therefore, the Committee recommended that beta-hydroxyfentanyl be controlled in Schedules I and IV of the Single Convention on Narcotic Drugs, 1961 and that Convention as amended by the 1972 Protocol.

Beta-hydroxy-3-methylfentanyl

Substance identification

Beta-hydroxy-3-methylfentanyl (CAS 78995-14-9), chemically N-[1-(beta-hydroxyphenethyl)-3-methyl-4-piperidyl]propionanilide, is also known as

ohmefentanyl, F 7302, NIH 10551 and OMF. The molecule has three chiral centres and there are eight stereoisomers and 4 pairs of racemates possible.

Similarity to already known substances and effects on the central nervous system

Beta-hydroxy-3-methylfentanyl has been classified as a relatively selective mu-type opioid receptor agonist with a profile similar to that of fentanyl. Its analgesic potency in rodents is estimated to be 25,000 times that of morphine. The drug has a rapid onset of action and a duration about 90 minutes. Like other mu-opioids, beta-hydroxy-3-methylfentanyl depresses respiration but to a lesser extent than fentanyl. The respiratory depression is reversible by nalorphine.

Dependence potential

Beta-hydroxy-3-methylfentanyl substitutes completely for morphine in morphine-dependent withdrawn monkeys. The substance is 25,000 times more potent than morphine in this regard. No human studies are available concerning the dependence potential of beta-hydroxy-3-methylfentanyl.

Actual abuse and/or abuse liability (likelihood of abuse)

Beta-hydroxy-3-methylfentanyl is one of the fentanyl analogues which have appeared in the illicit drug traffic since late 1979. Beta-hydroxy-3-methylfentanyl has been identified by a Drug Enforcement Administration (USA) laboratory in drug seizures and clandestine production has been demonstrated.

Therapeutic usefulness

At present, beta-hydroxy-3-methylfentanyl has no known therapeutic usefulness.

Recommendation

The Committee found that there was sufficient evidence to indicate that beta-hydroxy-3-methylfentanyl is liable to similar abuse as, and produces ill-effects similar to those seen with, drugs in Schedule I of the Single Convention on Narcotic Drugs, 1961 and that Convention as amended by the 1972 Protocol. The Committee rated the abuse liability of the substance as high. The degree of seriousness of the public health and social problems associated with the substances was found to be high and there is no known therapeutic usefulness. Therefore, the Committee recommended that beta-hydroxy-3-methylfentanyl be controlled in Schedules I and IV of the Single Convention on Narcotic Drugs, 1961 and that Convention as amended by the 1972 Protocol.

Thiofentanyl

Substance identification

Thiofentanyl (CAS 1165-22-6), chemically N-[1-[2-(2-thienyl)ethyl]-4-piperidyl]propionanilide, is also known as NIH 10505 and MCV 4567. No stereoisomers are possible.

Similarity to already known substances and effects on the central nervous system

Thiofentanyl has been classified pharmacologically as a relatively selective mu-type opioid receptor agonist with a profile similar to that of fentanyl. Its analgesic potency in rodents is estimated to be 60-100 times that of morphine.

Dependence potential

Thiofentanyl substitutes completely for morphine in morphine-dependent withdrawn monkeys. The substance is about 60 times more potent than morphine in this regard.

No human studies are available concerning the dependence potential of thiofentanyl.

Actual abuse and/or abuse liability (likelihood of abuse)

Thiofentanyl is one of the fentanyl analogues which have appeared in the illicit drug traffic since late 1979. Thiofentanyl has been identified by a Drug Enforcement Administration (USA) laboratory in drug seizures and clandestine production has been demonstrated.

Therapeutic usefulness

At present, thiofentanyl has no known therapeutic usefulness.

Recommendation

The Committee found that there was sufficient evidence to indicate that thiofentanyl is liable to similar abuse as, and produces ill-effects similar to those seen with, drugs in Schedule I of the Single Convention on Narcotic Drugs, 1961 and that Convention as amended by the 1972 Protocol. The Committee rated the abuse liability of the substance as high. The degree of seriousness of the public health and social problems associated with the substances was found to be high and there is no known therapeutic usefulness. Therefore, the Committee recommended that thiofentanyl be controlled in Schedules I and IV of the Single Convention on Narcotic Drugs, 1961 and that Convention as amended by the 1972 Protocol.

3-methylthiofentanyl

Substance identification

3-methylthiofentanyl (CAS 86052-04-2), chemically N-[3-methyl-1-[2-(2-thienyl)ethyl]-4-piperidyl]propionanilide, is also known as NIH 10546 and MCV 4591. There are two chiral carbon atoms in the molecule so that four stereoisomers and two racemates are possible.

Similarity to already known substances and effects on the central nervous system

The pharmacological profile of only one of the two racemates of 3-methylthiofentanyl ((±)-cis-3-methylthiofentanyl) has been examined. This racemate behaves as a relatively selective mu-type opioid receptor agonist. In rodent analgesic tests the substance is about 1,000 times more potent than morphine.

Dependence potential

3-methylthiofentanyl substitutes completely for morphine in morphine-dependent withdrawn monkeys. The substance is about 1,000 times more potent than morphine in this regard. No human studies are available concerning the dependence potential of 3-methylthiofentanyl.

Actual abuse and/or abuse liability (likelihood of abuse)

3-methylthiofentanyl is one of the fentanyl analogues which have appeared in the illicit drug traffic since late 1979. 3-methylthiofentanyl has been identified by a Drug Enforcement Administration (USA) laboratory in drug seizures and clandestine production has been demonstrated.

Therapeutic usefulness

At present, 3-methylthiofentanyl has no known therapeutic usefulness.

Recommendation

The Committee found that there was sufficient evidence to indicate that 3-methylthiofentanyl is liable to similar abuse as, and produces ill-effects similar to those seen with, drugs in Schedule I of the Single Convention on Narcotic Drugs, 1961 and that Convention as amended by the 1972 Protocol. The Committee rated the abuse liability of the substance as high. The degree of seriousness of the public health and social problems associated with the substance was found to be high and there is no known therapeutic usefulness. Therefore, the Committee recommended that 3-methylthiofentanyl be controlled in Schedules I and IV of the Single Convention on Narcotic Drugs, 1961 and that Convention as amended by the 1972 Protocol.

Annex II

NOTIFICATION FROM THE GOVERNMENT OF THE UNITED STATES OF AMERICA CONCERNING DELTA-9-TETRAHYDROCANNABINOL

Subject: Transfer of a substance from one Schedule to another Schedule annexed to the Convention

The Government of the United States of America, being a party to the 1971 Convention on Psychotropic Substances, refers to the following substance which is at present listed in Schedule I of the 1971 Convention on Psychotropic Substances:

Delta-9-tetrahydrocannabinol (delta-9-THC)

The United States Government has information relating to the above substance which, in the Government's opinion, may require the transfer of that substance from the Schedule in which it is at present listed, Schedule I, to Schedule II.

The Government of the United States of America transmits this notification to the Secretary-General of the United Nations, in accordance with paragraph 1 of article 2 of the 1971 Convention on Psychotropic Substances, in order to initiate the procedure provided for under that article.

The relevant information in support of this notification is annexed hereto.

1 December 1987

(Signed): Otis R. Bowen, M.D.
Secretary
Department of Health and Human Services

UNITED STATES OF AMERICA PROPOSAL TO TRANSFER DELTA-9-THC FROM SCHEDULE I TO SCHEDULE II

In support of its notification to transfer delta-9-tetrahydrocannabinol (delta-9-THC) from Schedule I to Schedule II of the 1971 Convention on Psychotropic Substances, the Government of the United States of America adds the following:

1. After a substantial period of clinical investigation, delta-9-THC has been demonstrated to be safe and effective in the treatment of nausea and vomiting experienced by certain patients receiving cancer chemotherapy. In recognition of that demonstrated therapeutic usefulness, the United States Food and Drug Administration (FDA) on May 31, 1985 approved for marketing a drug product whose active ingredient is delta-9-THC. On 13 May 1986, the United States Drug Enforcement Administration (DEA) completed a rescheduling action which resulted in the inclusion of a certain formulation of delta-9-THC in Schedule II of the United States Controlled Substances Act. This action permitted a formulation containing delta-9-THC in sesame oil to be marketed as an anti-emetic agent in the medical treatment of cancer patients receiving chemotherapy.

2. Currently, delta-9-THC is controlled internationally in Schedule I of the 1971 Convention on Psychotropic Substances because tetrahydrocannabinol and several identified isomers, including the delta-9 isomer, are subject to Schedule I control under that Convention. This is the most restrictive schedule of the 1971 Convention, and it has been traditionally reserved for substances with a high abuse liability and with very limited, if any, therapeutic usefulness. The Commentary on the 1971 Convention clearly indicates that when a determination to place a substance in Schedule I is made, a strong presumption exists that the substance has very little, if any, therapeutic value. The approval of delta-9-THC by the United States Government for administration as an anti-emetic to patients receiving cancer chemotherapy demonstrates that this substance now has been recognized as having therapeutic usefulness. By virtue of that event, delta-9-THC now differs significantly from substances placed in Schedule I of the 1971 Convention because it no longer conforms to the established criterion that Schedule I substances have very limited, if any, therapeutic usefulness.

3. The United States Government believes that delta-9-THC has a high potential for abuse although available data fail to demonstrate widespread actual abuse. Because delta-9-THC has now demonstrated therapeutic usefulness, we believe that continued international control of delta-9-THC in Schedule I of the 1971 Convention is no longer appropriate. Moreover, the United States believes that delta-9-THC should be transferred to Schedule II of the 1971 Convention because Schedule II provides the most reasonable level of control for this substance which now has accepted therapeutic usefulness.

4. The United States Government wishes to emphasize that although delta-9-THC is the principal psychotropic ingredient in the cannabis plant, delta-9--THC and cannabis are not the same. Cannabis, cannabis resin, cannabis extracts, and tinctures of cannabis are regulated under the Single Convention. The United States reaffirms the differences between these substances which are regulated under the Single Convention and the

substance, delta-9-THC. Our request relates only to the substance delta-9-THC and does not apply in any manner to cannabis or the derivatives of cannabis specified in the Single Convention.

5. The United States Government notes that it submitted a proposal to WHO in 1982 seeking to have delta-9-THC transferred from Schedule I to Schedule II of the 1971 Convention on Psychotropic Substances. The Director-General of WHO, based upon the findings of the 6th Review of Psychoactive Substances for International Control, responded to that proposal by recommending to the Secretary-General that delta-9-THC should remain in Schedule I for the present time "pending review of the activities and consequences of tetrahydrocannabinols." That review by WHO concluded that insufficient information was available to judge adequately the "degree of medical usefulness and the potential seriousness of the public health and social problems" that might result from transferring delta-9-THC to Schedule II of the 1971 Convention. The thirtieth session of the Commission on Narcotic Drugs noted that in view of WHO's recommendation, it need not take any further action. (See E/CN.7/1983/18, para. 190.)

6. The United States Government believes that sufficient information is now available on which to judge the degree of therapeutic usefulness and the potential seriousness of public health and social problems which might arise as a result of the medical use of delta-9-THC. Accordingly, the United States now affirms the following:

   (a) The formal marketing approval of delta-9-THC for administration to patients in the United States conclusively demonstrates the degree of usefulness of delta-9-THC in medical therapy as that phrase is applied in the 1971 Convention. Delta-9-THC is currently under evaluation in several other countries.

   (b) Both during the clinical investigative period which began in 1981 and since the approval to market delta-9-THC in the United States, there has been no evidence of a public health or social problem associated with the therapeutic use of the approved delta-9-THC product. On the contrary, the epidemiological tracking systems (i.e. the National Institute on Drug Abuse's DAWN system a/, FDA's Adverse Drug Reaction Reporting System, and DEA's STRIDE b/) customarily relied upon to demonstrate the existence of such problems in the United States have, to date, shown no evidence that delta-9-THC poses a public health or social problem. (See WHO document MNH/82.44, paragraph 11-3.)

7. The United States Government now believes that sufficient information exists to judge the merits of transferring delta-9-THC from Schedule I to Schedule II according to the criteria of the Convention and articulated by the WHO 6th Review of Psychoactive Substances. However, we are making no such statement, and we are seeking no such action with respect to any other substance within the class of tetrahydrocannabinoids.

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a/ Drug Abuse Warning Network.

b/ System to Retrieve Information from Drug Evidence.

Annex III

NOTIFICATION FROM THE DIRECTOR-GENERAL OF THE WORLD HEALTH ORGANIZATION CONCERNING DRONABINOL

The Director-General of the World Health Organization presents his compliments to the Secretary-General of the United Nations, and with reference to his note verbale (NAR/CL.3/1988, DND 411/1(2) WHO/ECDD 26) dated 28 January 1988, has the honour to inform him that the World Health Organization, in conformity with article 2, paragraph 6, of the Convention on Psychotropic Substances, 1971, has reviewed information pertaining to dronabinol (INN), defined as (6a*R*,10a*R*)-6a,7,8,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6*H*-dibenzo[*b*,*d*]-pyran-1-ol or (-)-*trans*-*delta*-9-tetrahydrocannabinol. There is sufficient evidence that dronabinol, which is currently in Schedule I of the aforementioned Convention and is listed as one of the stereochemical variants of *delta*-9-tetrahydrocannabinol, has therapeutic usefulness in selective cases but is otherwise likely to be abused so as to constitute a public health and social problem warranting maintaining it under international control.

Therefore, the World Health Organization recommends that dronabinol be changed from Schedule I to Schedule II of the Convention on Psychotropic Substances, 1971.

Summary of the recommendations arising out of the twenty-sixth Expert Committee on Drug Dependence

The twenty-sixth Expert Committee on Drug Dependence met at headquarters between 17 and 22 April 1989. Since the report of this meeting will be published in due course in the Technical Report Series, this paper gives details of the recommendations made to the Director-General of WHO.

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Delta-9-tetrahydrocannabinol

On 1 December 1987, the Government of the United States of America submitted to the Secretary-General of the United Nations a notification under article 2, paragraph 1, of the Convention on Psychotropic Substances, 1971 to transfer delta-9-tetrahydrocannabinol (delta-9-THC) from Schedule I to Schedule II of the Convention. a/ The Secretary-General of the United Nations in a note verbale (DND 421/12(1-37); DND 411/1(2)WHO) requested a recommendation of the Director-General of WHO.

The generic term delta-9-THC in the Convention refers to two racemates and four stereoisomers. However, the data presented by the United States of America along with its notification and the material presented in the Critical Review concerns a single stereochemical variant of delta-9-THC, (-)-trans-delta-9-tetrahydrocannabinol. Since little or no data exists on the racemates or other stereoisomers and the pharmaceutical preparation marketed in the United States contains only this one stereochemical variant, the Expert Committee reviewed only (-)-trans-delta-9-tetrahydrocannabinol. The following recommendations refer solely to this individual substance.

Substance identification

(-)-Trans-delta-9-tetrahydrocannabinol (INN Dronabinol, CAS 1972-08-3), chemically (6aR,10aR)-6a,7,8,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]-pyran-1-ol is also known as (6aR-trans)-6a,7,8,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo-[b,d]-pyran-1-ol, (-)-trans-delta-9-THC, (-)-trans-delta-1-tetrahydrocannabinol, and (-)-trans-delta-1-THC. Two trade names are known, Marinol and Deltanyne.

Two racemates and four stereochemical variants of the parent substance, delta-9-tetrahydrocannabinol, are possible.

The following review and recommendation apply solely to (-)-trans-delta-9-tetrahydrocannabinol, abbreviated as (-)-trans-delta-9-THC.

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a/ Letter of notification under article 2, paragraph 1, of the 1971 Convention on Psychotropic Substances, signed Otis R. Bowen, M.D. Secretary Department of Health and Human Services, 1 December 1987, annex I of Secretary-General's note verbale to the Director-General of the World Health Organization, 12 January 1988 [DND 421/12(1-37) DND 411/1(2)WHO].

Similarity to already known substances and effects on the central nervous system

(-)-Trans-delta-9-THC is identical to the major active principle of cannabis and cannabis resin, which are listed in Schedules I and IV of the Single Convention on Narcotic Drugs, 1961. It is listed in Schedule I of the Convention on Psychotropic Substances, 1971. It produces complex effects on the central nervous system. In small dose it produces stimulation, followed by sedation and in high doses it produces hallucinogenic effects. Non-therapeutic effects of (-)-trans-delta-9-THC may be considered essentially identical to those of marijuana and other centrally active cannabinoids. It produces significant decrements on a number of performance measures, including psycho- motor performance.

Dependence potential

A number of animal studies have been conducted to date but most studies failed to demonstrate reinforcing effects of (-)-trans-delta-9-THC except one study in monkeys. The subjective effects in human studies were reported to be moderately euphorigenic. Chronically administered high doses of (-)-trans-delta-9-THC apparently produce a state of physical dependence in rats. Withdrawal of (-)-trans-delta-9-THC causes a disruption of operant behaviour in monkeys maintained on the drug which does not occur until the second day of withdrawal and often lasts for over a week. This disruption of behaviour can be reversed by readministration of the drug. After abrupt discontinuation of high doses of (-)-trans-delta-9-THC given for 10 days or longer, human subjects exhibited some evidence of a withdrawal syndrome characterized by irritability, insomnia, restlessness, "hot flushes", diaphoresis, rhinorrhea, "loose stools", hiccoughs and anorexia.

Evidence of tolerance development to the behavioural and cardiovascular effects of the substance has been shown in human subjects. Animal studies have also confirmed a marked tolerance to the behavioural and hypothermic effects.

Actual abuse and/or abuse liability (likelihood of abuse)

(-)-Trans-delta-9-THC has been available for scientific and very limited medical use under close supervision for more than 15 years. The pharmaceutical product in sesame oil for oral use was marketed in 1986 in the United States of America. A number of cases of thefts and one case of "illicit purchase" have been reported. One attempt to synthesize the substance clandestinely was reported in the United Kingdom.

Drug Abuse Warning Network (DAWN, USA) data indicated a small number of emergency room or medical examiner mentions. Although the actual abuse of the marketed product is very limited, (-)-trans-delta-9-THC has a high abuse liability, as inferred from the abuse of cannabis and its products, with consequent public health and social hazards.

Therapeutic usefulness

(-)-Trans-delta-9-THC is being used in the United States of America and has been approved for marketing in Canada as an anti-emetic for use in cancer chemotherapy. It is effective in some cases in relieving severe nausea and vomiting refractory to the currently available anti-emetics. It may make possible treatment with anti-cancer drugs in some patients who might otherwise

refuse it. When applied in selected cases as an adjunct to cancer chemotherapy (-)-trans-delta-9-THC has a moderate to high therapeutic usefulness, but has otherwise no therapeutic role. (-)-Trans-delta-9-THC may produce a high incidence of transient side effects related to the central nervous system depending on the dose used.

Recommendation

On the basis of the available data concerning its pharmacological profile, dependence potential and actual abuse, the Committee rated the abuse-liability of (-)-trans-delta-9-THC as high and the therapeutic usefulness to be moderate to high when applied in selective cases as an anti-emetic adjunct to cancer chemotherapy, but otherwise has no therapeutic role. Although few public health and social problems are currently associated with the therapeutic use of (-)-trans-delta-9-THC, it should be noted that this substance is the active principle of cannabis and is capable of producing the same effects as the plant material. Thus, the Committee considered that (-)-trans-delta-9-THC, is likely to be abused so as to constitute a public health and social problem. In the light of this assessment, the Committee recommended rescheduling of the drug from Schedule I to Schedule II of the Convention on Psychotropic Substances, 1971. b/

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b/ Two members of the Committee, Professors M. Mubbashar and G. Lagier, representing a different point of view, felt that the decision on the recommendation should be deferred until further convincing data was available concerning the therapeutic usefulness of (-)-trans-delta-9-THC. Moreover, the recommendation might be misinterpreted and promote the abuse of cannabis and its extracts.

Annex IV

NOTIFICATIONS FROM THE DIRECTOR-GENERAL OF THE WORLD HEALTH ORGANIZATION CONCERNING N-HYDROXY MDA, N-ETHYL MDA, 4-METHYLAMINOREX AND MIDAZOLAM

N-hydroxy MDA

The Director-General of the World Health Organization presents his compliments to the Secretary-General of the United Nations and has the honour to inform him that the World Health Organization, in conformity with article 2, paragraphs 1 and 4, of the Convention on Psychotropic Substances, 1971, reviewed information pertaining to (±)-N-[alpha-methyl-3,4-(methylenedioxy) phenethyl]hydroxylamine and referred to as N-hydroxy MDA or N-OH MDA.

N-hydroxy MDA meets the criteria of article 2, paragraph 4(a), of the Convention, and there is sufficient evidence that the substance is, or is likely to be, abused so as to constitute a public health and social problem warranting placing it under international control.

Therefore, the World Health Organization recommends that N-hydroxy MDA be added to Schedule I of the Convention on Psychotropic Substances, 1971.

N-ethyl MDA

The Director-General of the World Health Organization presents his compliments to the Secretary-General of the United Nations and has the honour to inform him that the World Health Organization, in conformity with article 2, paragraphs 1 and 4, of the Convention on Psychotropic Substances, 1971, reviewed information pertaining to (±)-N-ethyl-alpha-methyl-3,4-(methylenedioxy) phenethylamine and referred to as N-ethyl MDA or MDE.

N-ethyl MDA meets the criteria of article 2, paragraph 4(a), of the Convention, and there is sufficient evidence that the substance is, or is likely to be, abused so as to constitute a public health and social problem warranting placing it under international control.

Therefore, the World Health Organization recommends that N-ethyl MDA be added to Schedule I of the Convention on Psychotropic Substances, 1971.

4-methylaminorex

The Director-General of the World Health Organization presents his compliments to the Secretary-General of the United Nations and has the honour to inform him that the World Health Organization, in conformity with article 2, paragraphs 1 and 4, of the Convention on Psychotropic Substances, 1971, reviewed information pertaining to (±)-cis-2-amino-4-methyl-5-phenyl-2-oxazoline and referred to as (±)-cis-4,5-dihydro-4-methyl-5-phenyl-2-oxazolamine or 4-methylaminorex.

4-Methylaminorex meets the criteria of article 2, paragraph 4(a), of the Convention, and there is sufficient evidence that the substance is, or is likely to be, abused so as to constitute a public health and social problem warranting placing it under international control.

Therefore, the World Health Organization recommends that 4-methylaminorex be added to Schedule I of the Convention on Psychotropic Substances, 1971.

Midazolam

The Director-General of the World Health Organization presents his compliments to the Secretary-General of the United Nations and has the honour to inform him that the World Health Organization, in conformity with article 2, paragraphs 1 and 4, of the Convention on Psychotropic Substances, 1971, reviewed information pertaining to midazolam (INN) and defined as 8-chloro-6-(o-fluorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepine.

Midazolam meets the criteria of article 2, paragraph 4(a), of the Convention, and there is sufficient evidence that the substance is, or is likely to be, abused so as to constitute a public health and social problem warranting placing it under international control.

Therefore, the World Health Organization recommends that midazolam be added to Schedule IV of the Convention on Psychotropic Substances, 1971.

Summary of the recommendations arising out of the twenty-sixth Expert Committee on Drug Dependence

The twenty-sixth Expert Committee on Drug Dependence met at headquarters between 17 and 22 April 1989. Since the report of this meeting will be published in due course in the Technical Report Series, this paper gives details of the recommendations made to the Director-General of WHO.

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Analogues of MDA

N-Hydroxy MDA

Substance identification

(±)-N-hydroxy MDA (CAS 74698-47-8), chemically N-[alpha-methyl-3,4-(methylenedioxy)phenethyl]hydroxylamine, is also known as 3,4-methylenedioxy-N-hydroxyamphetamine, N-hydroxy-3,4-methylenedioxyamphetamine, N-OHMDA, N-hydroxy-3,4-methylenedioxyphenylisopropylamine and 1-(3,4-methylenedioxyphenyl)-2-hydroxyaminopropane. There is one chiral carbon atom in the molecule so that two stereoisomers and one racemate are possible.

Similarity to already known substances and effects on the central nervous system

In rodent studies, (±)-N-hydroxy MDA was shown to be a psychomotor stimulant. In drug discrimination studies in rats, the substance did not generalize to either d-amphetamine or (±)-1-(2,5-dimethoxy-4-methylphenyl)-2-aminopropane (DOM). In humans, it was reported to have psychotomimetic activity at relatively high doses.

Dependence potential

In self-administration studies in the baboon, (±)-N-hydroxy MDA was reinforcing. The substance produced an amphetamine-like pattern of intake. The same laboratory previously reported that (±)-N-methyl-alpha-methyl-3,4-(methylenedioxy)phenethylamine (MDMA) was self-administered by baboons in a similar experiment.

Actual abuse and/or abuse liability (likelihood of abuse)

No data is available on actual abuse. (±)-N-hydroxy MDA has been identified in illicit traffic both in the USA and Europe. Clandestine production has been reported.

Therapeutic usefulness

There is no known therapeutic usefulness for (±)-N-hydroxy MDA.

Recommendation

On the basis of the data concerning its pharmacological profile, dependence potential, and actual abuse, the Committee rated the likelihood of abuse of (±)-N-hydroxy MDA as moderate. The degree of seriousness of the public health and social problems associated with the substance was found to be low at the present time and it has no known therapeutic usefulness.

The Committee found that there was sufficient evidence that (±)-N-hydroxy MDA is being, or is likely to be, abused so as to constitute a public health and social problem warranting the placing of the substance under international control.

In the light of this assessment, the Committee recommends that (±)-N-hydroxy MDA be controlled under Schedule I of the Convention on Psychotropic Substances, 1971.

N-Ethyl MDA (MDE)

Substance identification

(±)-N-ethyl MDA (MDE) (CAS 14089-52-2), chemically N-ethyl-alpha-methyl-3,4-(methylenedioxy)phenethylamine is also known as 3,4-methylenedioxy-N-ethylamphetamine, N-ethyl-3,4-methylenedioxyamphetamine, Eve, MDEA, N-ethyl-3,4-methylenedioxyphenylisopropylamine, 1-(3,4-methylenedioxyphenyl)-2-ethylaminopropane and 3,4-methylenedioxyethamphetamine. There is one chiral carbon atom so that two stereoisomers and one racemate are possible.

Similarity to already known substances and effects on the central nervous system

(±)-N-ethyl MDA has psychomotor stimulating properties in rodents and produces neurotoxicity which results from its damaging effects on serotonergic systems in the brain. In discrimination studies in rats, (±)-N-ethyl MDA generalizes to MDMA but not to d-amphetamine or DOM. Psychotromimetic effects have been observed in humans. Thus, (±)-N-ethyl MDA has a pharmacological profile similar to that of MDMA.

Dependence potential

In a baboon self-administration study, (±)-N-ethyl MDA was found to have reinforcing properties. There are no studies available on dependence potential in human subjects.

Actual abuse and/or abuse liability (likelihood of abuse)

There is evidence from the Drug Abuse Warning Network (DAWN, USA) data for abuse, and two deaths have been reported in which (±)-N-ethyl MDA was detected in body fluids, along with other drugs. The substance has been identified in drug seizures in the USA, Canada and the Federal Republic of Germany. Clandestine production has been demonstrated. There is some evidence that (±)-N-ethyl MDA may pose a significant risk to public health due to its neurotoxicity.

Therapeutic usefulness

There is ro known therapeutic usefulness for (±)-N-ethyl MDA.

Recommendation

On the basis of the available data concerning its pharmacological profile, dependence potential and actual abuse, the Committee rated the likelihood of abuse of (±)-N-ethyl MDA as moderate. The degree of seriousness of the public health and social problems associated with the substance was found to be high and it has no known therapeutic usefulness.

In the light of this assessment, the Committee recommends that (+)-N-ethyl MDA be controlled under Schedule I of the Convention on Psychotropic Substances, 1971.

Analogue of aminorex

4-Methyl aminorex

Substance identification

4-methylaminorex (CAS 3568-94-3), chemically 2-amino-4-methyl-5-phenyl-2-oxazoline is also known as McN-822, euphoria, U4Euh, ICE, d,l-cis-2-amino-4-methyl-5-phenyl-2-oxazoline, d,l-erythro-2-amino-4-methyl-5-phenyl-2-oxazoline, (+)-cis-2-amino-4-methyl-5-phenyl-2-oxazoline and (+)-erythro-2-amino-4-methyl-5-phenyl-2-oxazoline. There are two chiral carbon atoms so that four stereoisomers and two racemates are possible.

Similarity to already known substances and effects on the central nervous system

4-methylaminorex (cis racemate) is a potent psychomotor stimulant. Its actions are similar to those produced by amphetamine. It stimulates spontaneous activity in mice, has sympathomimetic and central stimulating effects in dogs and generalized to d-amphetamine in discrimination studies in rats. Its potency is about one half that of d-amphetamine and it produces a lower degree of stimulation.

Dependence potential

In self-administration studies in rhesus monkeys 4-methylaminorex (cis racemate) had potent reinforcing activity. All animals self-administered the substance at rates comparable to that of cocaine. No human studies are available concerning the dependence liability of 4-methylaminorex (cis racemate).

Actual abuse and/or abuse liability (likelihood of abuse)

No epidemiological data of actual abuse is available but there have been individual case reports. One death has been reported with significant blood levels of 4-methylaminorex (cis racemate) and diazepam. There is evidence of illicit traffic in the USA and clandestine production has been demonstrated.

Therapeutic usefulness

There is no known therapeutic usefulness for 4-methylaminorex (cis racemate).

Recommendation

On the basis of available data concerning its pharmacological profile, dependence potential and actual abuse, the Committee rated the likelihood of abuse of 4-methylaminorex (cis racemate) as moderate to high. The degree of seriousness of the public health and social problems associated with the substance was found to be moderate and it had no therapeutic usefulness.

The Committee found that there was sufficient evidence that 4-methylaminorex is currently being, or is likely to be, abused so as to constitute a public health and social problem warranting the placing of the substance under international control.

In the light of this assessment, the Committee recommends that 4-methylaminorex (cis racemate) be controlled under Schedule I of the Convention on Psychotropic Substances, 1971.

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Midazolam

Substance identification

Midazolam (INN, CAS 59467-70-8), chemically 8-chloro-6-(o-fluorophenyl)-1-methyl-4H-imidazo[1,5-a][1,4]benzodiazepine, is also known as Dormicum, Dormoniol, Hypnovel, Versed, Dormonid and Flormidal. No stereoisomers are possible.

Similarity to already known substances and effects on the central nervous system

Midazolam is a benzodiazepine with the full range of the group specific CNS depressant effects of benzodiazepines, such as anxiolytic, anti-convulsant, sedative-hypnotic, muscle relaxant effects etc. In animal experiments, midazolam is as efficacious as diazepam in most of its pharmacological effects, but has a more rapid onset and shorter duration of action. Clinical studies suggest that it is twice as potent as diazepam in its sedative-hypnotic effects. Midazolam is water insoluble, but its salts are soluble. It has an elimination half-life of approximately 2-2.5 hours in humans. Therapeutic use of midazolam, particularly at higher doses or in the elderly, may result in cardiopulmonary disturbances.

Dependence potential

Midazolam has been demonstrated to be reinforcing in animal studies. In physical dependence studies in animals, midazolam substituted for phenobarbital and produced barbiturate-like withdrawal signs.

Actual abuse and/or abuse liability (likelihood of abuse)

Abuse of midazolam is reported in several countries. There is also evidence of illicit trafficking and diversions from a number of countries. The Committee noted reports of severe cardiopulmonary adverse effects and some deaths.

Therapeutic usefulness

Midazolam is currently available in at least 33 countries. It is marketed as tablets for use in sleep disturbances and as a parenteral preparation for use as an adjunct to anesthesia.

Recommendation

On the basis of the available data concerning its pharmacological profile, dependence potential and actual abuse, the Committee rated the abuse-liability of midazolam as moderate and the therapeutic usefulness as moderate to high. Some public health and social problems are currently associated with the use of midazolam. As with all benzodiazepine agonists studied to date, it can be inferred from the preclinical studies that midazolam is capable of producing a state of dependence in human subjects similar to that observed with diazepam. In addition, the Committee noted that the availability of the substance as an

injectable enhances the likelihood of abuse. Thus, the Committee considered that midazolam is likely to be abused so as to constitute a public health and social problem warranting the placing of the substance under international control. In the light of this assessment, the Committee recommended scheduling of the drug in Schedule IV of the Convention on Psychotropic Substances, 1971.

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